Mixed-formalism hierarchical modeling and simulation with BioRica

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Challenge of reuse biological models

- Many models are produced for biological phenomena of different kinds. Models are complementary or competing.
- Each model is experimentally validated, and this is expensive.
- Numerical representations of biological systems are constructed using a number of different formalisms and simulation techniques.
- Need to reuse and compose existing models without revalidation.

Hierarchical modelling

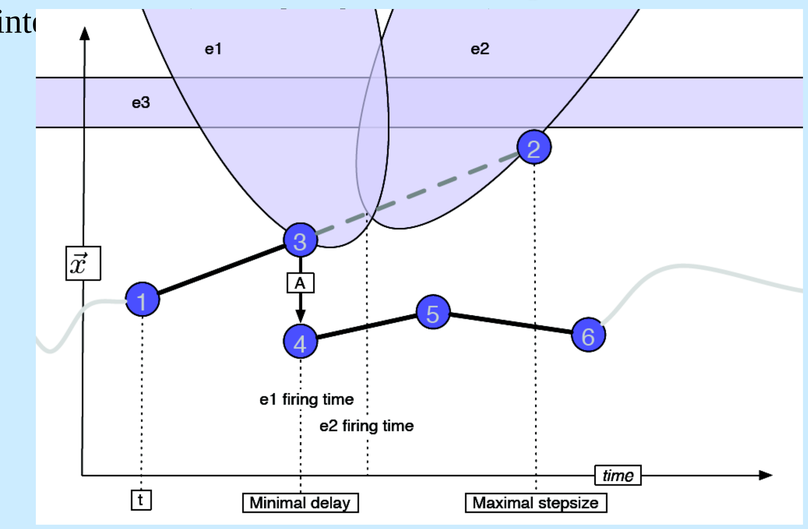
- Models are decomposed into hierarchical collection of nodes, each with it own local behaviour (De Alfaro et al. 2001).
- This gives a methodical way to combine existing models into a more complete one.
- Exists a rigorous semantics for hierarchical combination.
- BioRica (Soueidan et al. 2007) is a language for describing hierarchical modelling, derived from AltaRica (Arnold et al. 2000).
- Existing models in different formalisms (automata, ODE), and different notations like SBML (Hucka et al. 2010) can be combined into a BioRica model.

Stochastic transition systems (De Alfaro et al. 2001)

- Biological systems are not deterministic.
- Stochastic transition systems allows timed events and non deterministic transition relations.
- Extend transition system with random timers : random variable with a distribution specified by the stochastic labelling.
- Add stochastic behaviour to describe the likelihood that an event fires when it is activated concurrently with another event.

Combining continuous and discrete behaviours

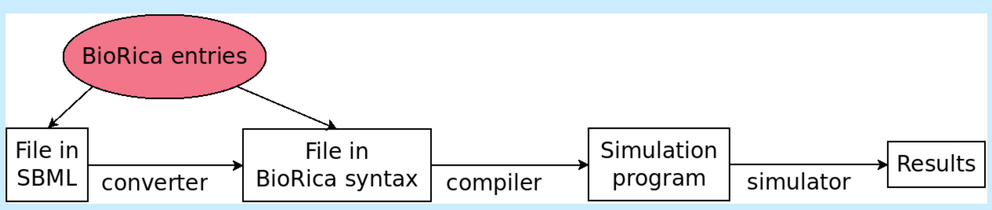
- Challenge is efficiently combining the computation of the behaviours.
- Simulation deals with continuous time and allows for discrete events that roll back the time according to these discrete int



- The numerical integrator advances between t (**point 1**) and the maximal stepsize defined by an adaptive integration algorithm (**2**).
- The guards of events *e1*, *e2* are satisfied.
- The regions where guards are satisfied are shaded.
- The firing time of *e1* (**3**) is used to reset the simulator after the discrete transition A (**4**)

BioRica

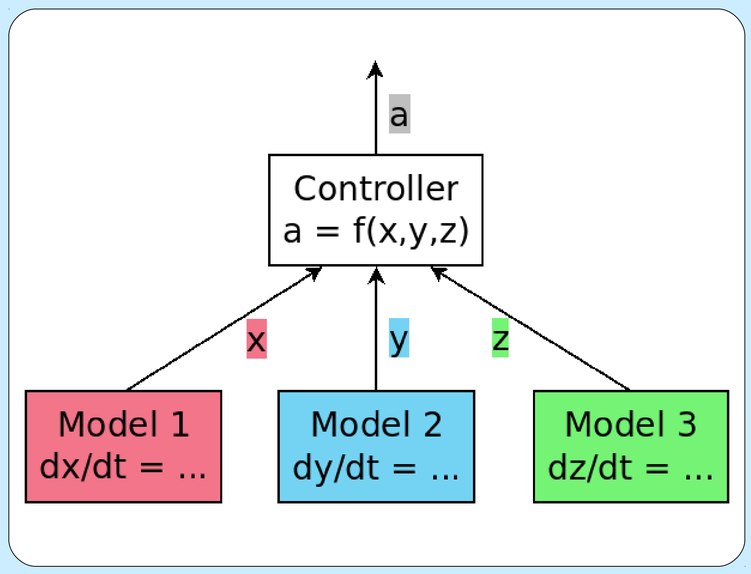
- A platform for hierarchical mixed-formalism modeling of complex systems in biology.
- Contained a converter, a compiler and a simulator.

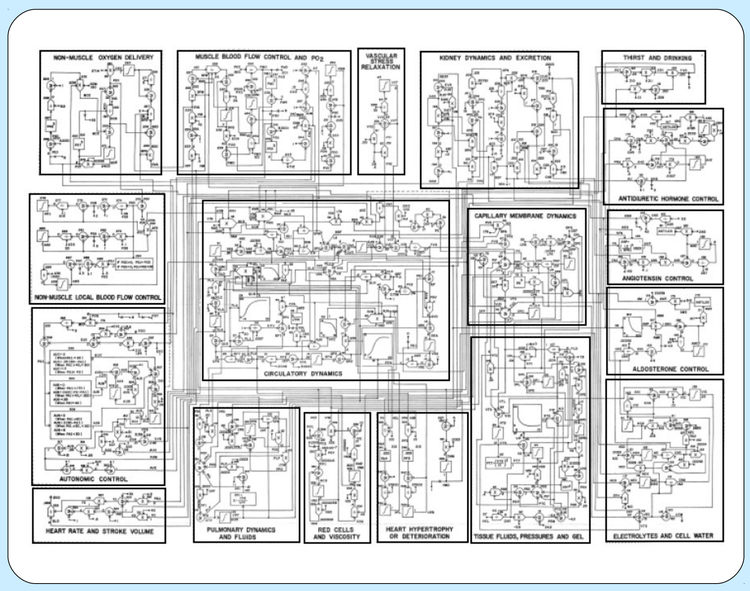


Practical examples

Needs :
Intelligent combination of models without refinement.

Solution : Numerical models and a discrete controller.





Needs :
Integrate modules with different time scales.

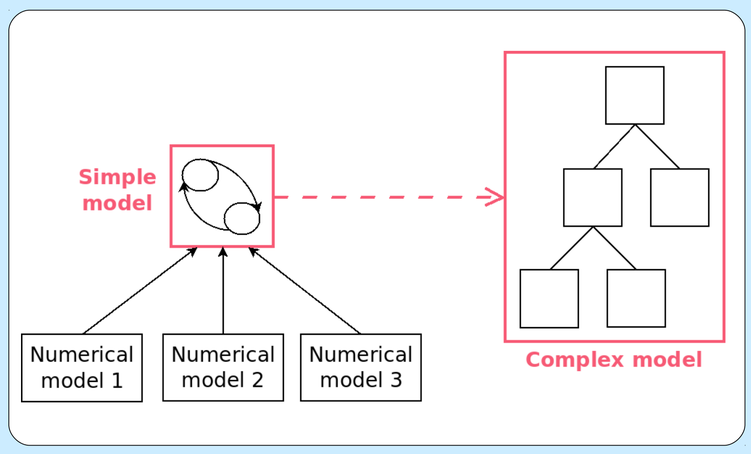
Solution : Hierarchical representation of the model.

Canonical example : Guyton circulatory model (Guyton et al. 1972) : an extensive mathematical model of human circulatory physiology.

Needs :
Successive refinement.

Solution : Convert a simple automate to a complex model.

Example : Replace simple physical switch by model of a cell signalling pathway



Availability

- SBML converter, compiler, simulator and examples.
- Available soon : http://biorica.gforge.inria.fr/

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